

Chronopharmacology and its importance in the therapy of Rheumatoid Arthritis: A Systematic Review

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Abstract— Rheumatoid arthritis (RA) is a chronic, autoimmune and inflammatory disease that primarily affects the joints. The symptoms of RA are most pronounced in the morning, fluctuating throughout the day. Studies report cases of failure in current RA therapy. With the intention of collaborating to reduce these failures, it is suggested to implement the knowledge related to Chronopharmacology. Thus, the aim of this study is to highlight the importance of Chronopharmacology in the efficiency of pharmacological treatment of RA through a systematic review. The search for scientific studies related to the theme was carried out in the databases PubMed, Lilacs, Scielo and Google Scholar from August 2019 to April 2020. This work brought together studies that demonstrated aspects related to the topic, and also allowed to bring possible solutions for application of this science in the clinical practice of Pharmacists and other health professionals. The information obtained in this research revealed that the administration of the drugs used by patients with RA according to the circadian rhythm provided a significant improvement in the symptoms, in addition to favoring the regression of the disorder. However, there is a need for further studies to show that the uses of disease-modifying antirheumatic drugs (DMARDs) have their action more potentiated when chronopharmacological principles are used.

I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease of the joints. This inflammation is caused by alterations in the body's defense system¹. Defined as an autoimmune disorder, the severity of RA can be graded as mild, moderate or severe, causing acute and chronic inflammation accompanied by a proliferative and destructive process of the joint tissues, which may eventually result in joint deformity².

The morbidity and severity of rheumatoid arthritis are more significant when involve other organs of the patients, thereby causing a decrease in life expectancy and

an inability to perform daily activities^{1,3,4}. Previous estimates reported that, in Brazil, 1.3 million people are affected by the life-threatening condition⁵. Interestingly, the frequency is 2 to 3 times higher in women over 40 years old, with a high incidence in the fifth decade of life⁶.

Inflammation of rheumatoid arthritis is not constant, but oscillates during the day. However, stiffness, edema and pain are more intense in the morning, thus directly influencing the routine of individuals, and resulting in a decrease in their functional capacities⁷. Ohdo et al.⁸ affirm that the administration of drugs when they are more effective or better tolerated is an alternative to

increase the efficacy of the pharmacotherapy used by these patients. This variation is associated with chronopharmacology, a science that aims to assess the activity of drugs according to biological rhythms, for example, the sleep-wake cycle⁷.

The term chronopharmacology was created in the early 1960s, and its first application to clinical medicine was in the timing of steroid therapy to mitigate both real and potential toxicity, and to increase its effectiveness⁹. Dallmann et al.¹⁰ reported that various physiological aspects of mammals, including sleep, breathing and arterial tensions, vary according to the time of day, being regulated by internal biological rhythms.

Chronopharmacology aims to explore the predictable changes in the therapeutic action of drugs depending on the time of administration on a 24-hour scale^{7,8,11-13}. Among the different organic functions, there is a series of rhythms that vary throughout the day, which are classified as circadian rhythms (circa = “close” or “about”, dian = “day”)¹⁴.

Chronopharmacology is of paramount importance, since the kinetics and dynamics of drugs are directly affected by biological rhythms and the time of administration, which are crucial factors for the pharmacological effect¹⁵. Therefore, it is necessary to consider that, after being used, a medication may undergo changes in its effect according to the moment, within the circadian cycle, when it reaches the target organ^{8,16-18}.

Previous studies reported cases of failure in current therapy of rheumatoid arthritis¹⁹⁻²². Rubbert-Roth et al.²³ stated that approximately 30 to 40% of patients discontinue treatment with anti-TNF due to primary failure, secondary loss of response or intolerance. Patients can also stop treatment owing to side effects. Other possible reasons for variability include adherence problems, cessation of methotrexate when synthetic treatment is initiated or differences in the pharmacokinetics of drugs²³. Indeed, adverse events and lack of efficacy are the most important reasons for ending the use of disease-modifying drugs²⁴.

From this perspective, there is a need to discuss the relevance of chronopharmacology in the therapy of rheumatoid arthritis, which may correlate the influence of chronopharmacology on the therapeutic success of patients with such disease. Thus, the aim of the present systematic review is to assess the importance of chronopharmacology

in the efficiency of RA drug treatment, contributing to its adherence and decreasing treatment tolerance.

II. METHODOLOGY

The present research is a systematic review of the literature organized in the following stages: choice and delimitation of the study; establishment of keywords and inclusion and exclusion criteria, and analysis of the information collected. The search was conducted through the electronic databases Medline/PubMed, Lilacs, Google Scholar and Scielo, aiming to find a significant number of related studies from August 2019 to April 2020. The following descriptors, in English and Portuguese languages, were used: “Chronopharmacology and Rheumatoid Arthritis” and “Chronopharmacology and Chronic Inflammation”. An initial analysis was performed based on the abstract of all papers that met the inclusion criteria. After reading the abstracts, the selected articles were obtained in full to be examined according to the established inclusion criteria. The inclusion criteria were: studies with human subjects, complete articles published in Portuguese or English languages in the period from 2010 to 2020 and which are related to the topic of the study. The exclusion criteria were: review articles, *in vitro* studies, articles that are not related to the addressed topic and that are outside the mentioned period of publication or in other languages than those aforementioned.

III. RESULTS AND DISCUSSION

Complying with the previously established methodology, the search for articles yielded 23 references. These searches were carried out based on keywords directly associated with the central theme of this study. Firstly, 10 articles were retrieved in the Pubmed database. After the initial analysis by reading the abstracts, 3 articles were selected and 7 were excluded for being review articles. 13 articles were identified in the Google Scholar database, and after reading the titles and abstracts, 5 articles were selected and 8 were excluded according to the inclusion criteria. No articles were found in Lilacs and Scielo databases.

Then, the 8 articles initially selected after reading the abstracts were eligible for full appraisal, and only 3 met the inclusion criteria. The studies selected for the review are demonstrated according to the PRISMA model, described in Figure 1.

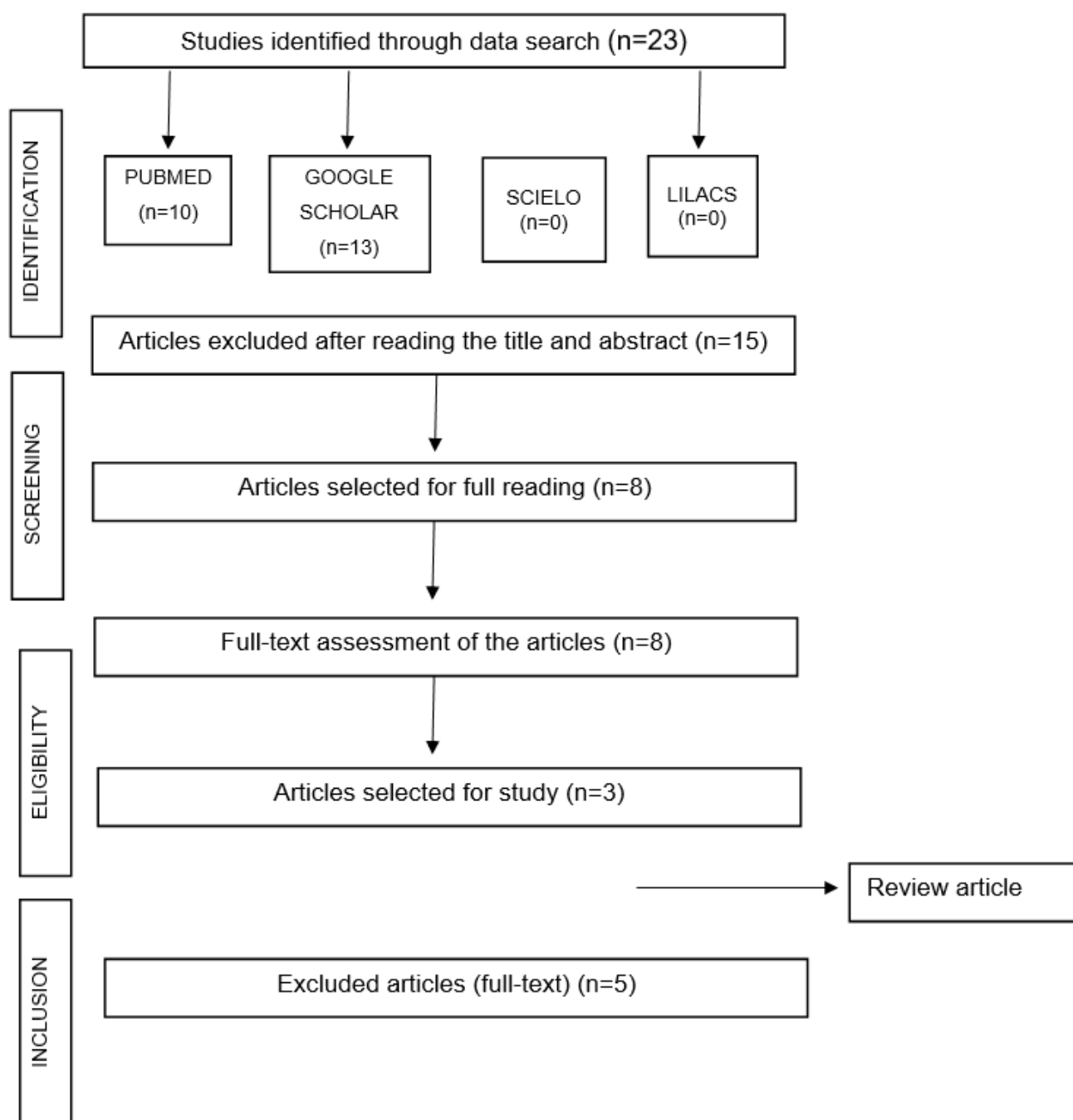


Fig.1 - Flowchart of the selection of articles

Source: The authors, 2020.

The selected studies (Chart 1) were performed in diverse countries, being one in Germany, one in the United States and onereseach conducted in two different countries, Germany and Poland. Regarding these 3 studies, the drug used for clinical tests in volunteer patients was a modified-release formulation of the oral corticosteroid class, being administered at night during the entire

treatment period (Table 1). After completing the total sum of patients who participated in the 3 studies, it was found that 647 patients had active RA, defined as the target audience of each study. Of these, only 581 patients completed the research. Each volunteer started the study without changing their therapy with other anti-rheumatic drugs.

Chart 1 - Articles selected after inclusion and exclusion criteria

Title of the article, authorship and year	Type of study	Objective
Aiming at pathophysiological rhythms: chronotherapy with prednisone exhibits sustained efficacy in rheumatoid arthritis ²⁵ .	Double-blind	To investigate the safety and long-term effectiveness of chronotherapy with a new modified-release prednisone for up to 12 months.
Effect of new therapeutic glucocorticoids on circadian rhythms of hormone and cytokine levels in rheumatoid arthritis ²⁶ .	Clinical tests	To study the circadian dynamics of serum IL-6, other cytokines and cortisol in 9 patients before and after 2 weeks of therapy, using a formulation that releases prednisone at 2 am (after ingestion at 10 pm).
Chronotherapy with low dose of prednisone for rheumatoid arthritis: a randomized clinical trial (CAPRA-2) ²⁷ .	Double-blind	To evaluate the efficacy and safety of low-dose prednisone chronotherapy using a new modified-release formulation for the treatment of rheumatoid arthritis.

Source: Search performed by the authors in databases. Salvador, 2019.

Table 1 - Chronopharmacotherapeutic studies in patients with rheumatoid arthritis

Therapeutics	Number of patients with RA	Duration	Administration hour	Bibliographic reference
MR prednisone 2 to 10mg per day	288	9 months	At 21:30 and at 22:30	Buttgereit et al. ²⁵
MR prednisone 5mg	9	14 days	At 10pm	Kirwan et al. ²⁶
MR prednisone 5mg	350	12 weeks	After dinner	Buttgereit et al. ²⁷

Source: The authors, 2020.

MR: modified-release.

The main joint manifestation presented by patients affected by rheumatoid arthritis is morning stiffness. This symptom is responsible for causing difficulty and limiting movement²⁸. In the selected articles,

significant improvements in morning stiffness were greater in the group using prednisone chronotherapy, being represented by 241 patients (Figure 2).

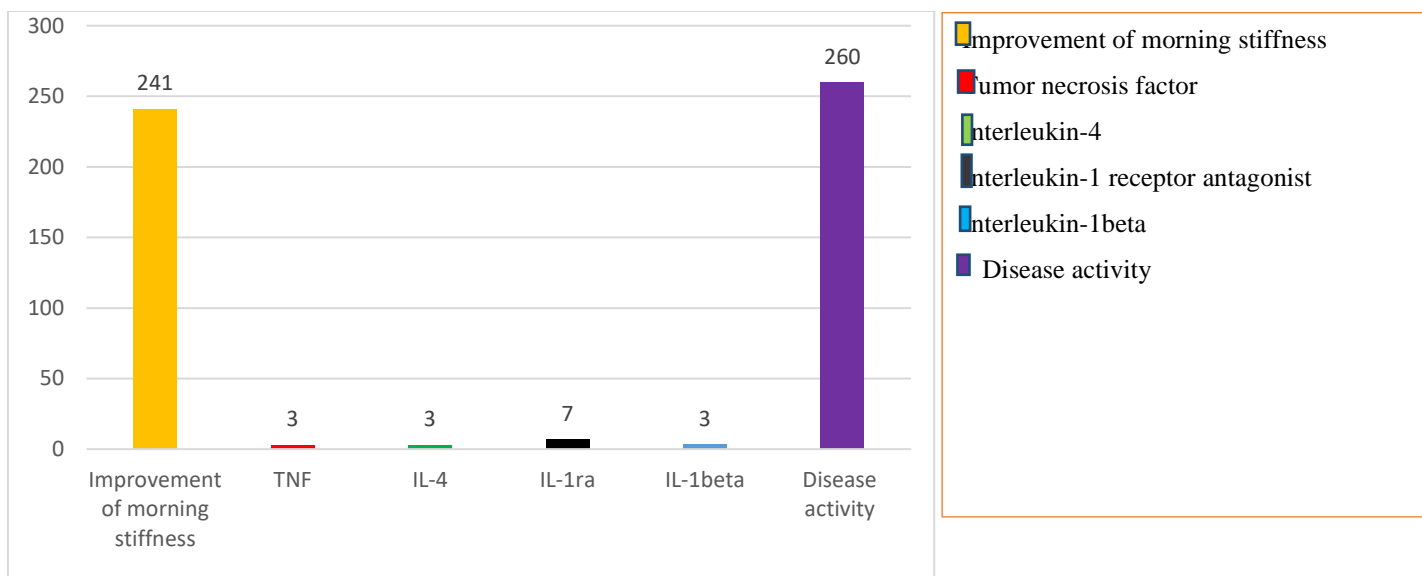


Fig.2 - Improvements revealed by patients after using modified-release prednisone at night.

Source: The authors, 2020.

The studies exhibited that, after treatment with MRprednisone, only 3 patients had high levels of TNF. Additionally, high levels of interleukin-4 and interleukin-1 beta were observed, as shown in Figure 2. According to Kirwan et al.²⁶, these data suggest that a subgroup of patients is resistant to glucocorticoids in general. Besides that, in a precise and quantified study²⁷, it was reported that about a quarter of patients may have clinical and cellular resistance to glucocorticoids. Further, 7 patients had levels of IL-1RA (Figure 2), which is secreted by macrophages and acts as a natural inhibitor of IL-1³⁰ activity. In the study by Buttgereit et al.²⁷, TNF levels remained unchanged, while Buttgereit et al.²⁵ did not assess this parameter. According to Lucas et al.³¹, the tumor necrosis factor-alpha is one of the most important cytokines involved in rheumatoid arthritis. In fact, the Tumor Necrosis Factor (TNF) is a key regulator in the inflammatory cascade, being responsible for the activation of lymphocytes, stimulation of the release of proteolytic enzymes by macrophages and production of other inflammatory cytokines, such as IL-6 and IL-3. Normally, the body naturally blocks the excess of TNF. However, in rheumatic disease, it remains active and induces more inflammation³².

In rheumatoid arthritis, inflammation of the synovial membrane is caused in part by excessive production of cytokines, including interleukin IL-6. IL-6 is increased in RA, correlating with disease activity^{28,33}. Importantly, the selected studies demonstrated that patients who used the treatment involving chronotherapy showed a greater reduction in the levels of this cytokine. The study by Kirwan et al.²⁶revealed that the only cytokine that

hadmeasurable circadian variation was IL-6, in addition to stating that morning stiffness and pain in rheumatoid arthritis are accompanied by an increase in serum interleukin-6 (IL-6) from 2:00 am to 7:00 am. In this same study, a surprising observation was the circadian pattern of cortisol. After two weeks of treatment with MR prednisone with nighttime-release, patients had lower serum cortisol in the afternoon and at night, with an earlier and more pronounced increase of this hormone in the early morning.

Cortisol, also known as stress hormone, is an intrinsic hormone of great importance, being secreted by the adrenal glands daily. According to the circadian rhythm, the cortisol level should be low at night. The hormone has a rhythmic secretion that can be altered due to disturbances in the circadian system³⁴. Chronic variations in its concentrations can lead to different disorders, including diabetes, depression, cancer and arthritis. Ribeiro³⁵ affirms that the production of cortisol by the hypothalamic-pituitary-adrenal axis during the active phase interrupts the secretion of pro-inflammatory cytokines. Thus, this process reveals that the circadian rhythm has a strong impact on autoimmune diseases and their treatment.

Pain management is the highest priority for patients affected by RA^{36,37}. Heiberg et al.³⁶reported that pain is the factor in which almost 70% of patients would like to see progress. According to Walsh et al.³⁸, pain not only affects patients directly, but also indirectly contributes to the psychological and social impact of RA. Pain assessment and disease activity have also been assessed in previous studies^{25,27}. Based on a functional

capacity score questionnaire (DAS28), it was found that 260 patients showed clinically relevant improvements in this parameter (Figure 2).

The American College of Rheumatology (ACR) criteria for RA are often used as aids in diagnosis³⁹. ACR rates are scales for measuring changes in rheumatoid arthritis symptoms³. In the selected articles, there was a significant improvement in ACR20 and ACR50 response rates versus MR prednisone^{25,27}. As shown in Figure 3, 85% of the patients who were treated with MR prednisone exhibited an improvement of 20% in the ACR20 score and 22% achieved an ACR50 response.

The studies conducted by Paolino et al.⁴⁰ and Naafs⁴¹ corroborated with that by Buttgerit et al.²⁷, since the authors suggested that the optimal time for glucocorticoid treatment is at night, in order to mimic the normal circadian rhythm of cortisol secretion. Still according to Naafs⁴¹, the symptoms of RA were attenuated when DMARDs were used with the prolonged release formulation, in comparison to the use of DMARDs in

monotherapy, emphasizing the possible promising future of chronopharmacology for the treatment of RA, as well as for other pathologies.

It is worthwhile noting that the use of chronopharmacology concepts in the treatment of rheumatoid arthritis is of great relevance, as it has contributed to the increase in the efficacy of the drugs, optimizing the time and dosage of them, besides providing significant improvement in symptoms, thus enabling a better quality of life for patients affected by the disease and its regression⁴².

The findings of the study indicated that, in order to increase the therapeutic effects of drugs and minimize their side effects, it may be useful to choose the most appropriate time of day for administration, in addition to pointing out that, to perform this process, the rhythmic markers could be monitored. Nainwal et al.¹² also affirm that drug administrations must be carried out at the moments when they are best tolerated in order to increase the efficacy of pharmacotherapy.

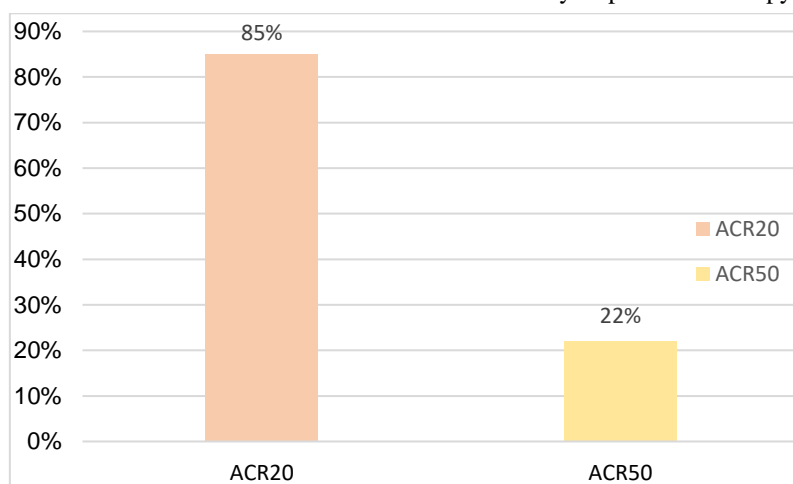


Fig.3 - Proportion of patients with responses related to the ACR criterion (American College of Rheumatology score).

Source: The authors, 2020.

According to Alsaikhan et al.⁴³, studies have evaluated the extent to which it is possible to use chronopharmacology in the medical field. This science has still been little applied due to the insufficient knowledge of professionals, including pharmacists. The pharmaceutical professional plays a pivotal role in society, being responsible for the well-being and quality of life, working to prevent issues related to the use of drugs⁴⁴. This professional has a remarkable role in providing information related to medications, including advice on the ideal time to administer them. In this context, it is essential to include the concepts of chronopharmacology during drug counseling⁴⁵.

One of the reasons for this lack of knowledge on the part of professionals is related to the little or no approach of this science in universities⁴⁵. The conventional curricula of pharmacy and medical schools are based on the biological concept of homeostasis (in which the internal physiological environment of the human body remains in a relatively constant state) as the only governing principle of biology and of the behavior of drugs⁴⁶. Thus, there is a need to include in the degree programs in Pharmacy and Medicine, for instance, the concepts associated with circadian rhythms that affect the administration of drugs.

Educational and professional training in chronotherapy, especially in the field of chronopharmacology to improve the knowledge, access to information, skills and competence of Pharmacists, as well as other health professionals in clinics, is also very useful to afford the safe and effective use of drugs in some cases⁴⁵. In order to choose the time of administration, it is important to discuss with the patient the time of day that symptoms appear more frequently⁴⁷.

According to Chen⁴⁸, the development of new drugs based on chronopharmacology has also been extensively explored, whose focus is to investigate circadian rhythms as a therapeutic target. Chen⁴⁸ states that the investigation of representative drug candidates that present targets in the circadian clock occurs with the use of approaches that involve chemical screenings that employ phenotypic assays measuring circadian reporter expression and the profile of some compounds in altering the cardinal characteristics of the circadian rhythm, period, phase and amplitude.

It is worth mentioning that some drugs already have this chronopharmaceutical technology. Some examples and applications are: in parenteral routes, which include chronomodulating infusion pumps, controlled-release microchip, transdermal drug delivery system for chronopharmaceutical applications, administration of drugs containing nanoformulations and oral administration⁴⁹, such as the CodaTM system (Chronotherapeutic Oral Drug Absorption System), a controlled-release system, in which the tablet has several layers, soluble and insoluble in water, with the drug positioned in the center and, as the water penetrates the system, the layers change and release the drug^{11,50}.

According to Tamosiunas¹¹, studies related to biological rhythms and their application in clinical practice, in addition to approaching the true human nature, will allow to plan treatments and the way to envision the health-disease process from another perspective. The author also reports that understanding the periods of greatest vulnerability or susceptibility to external agents or to the action of drugs can help to modulate the morbid processes more effectively and to improve the relationship between the risk and benefit of the drugs used.

IV. CONCLUDING REMARKS

Patients with rheumatoid arthritis present the most pronounced symptoms during the morning due to the inflammatory process involved with the circadian rhythm. For this reason, the studies herein showed that the pharmacological treatment of these patients must also

follow this pattern, being more effective when administered at night.

Patients with rheumatoid arthritis use a variety of drug classes. However, it was observed that the studies mentioned oral corticosteroids, a pharmacological class widely used by these patients. In turn, there was a need for further studies that addressed DMARDs, associating the potentiation of their effects with the use of chronopharmacology. Moreover, a limited number of articles met the inclusion criteria of this research, which is due to few studies in the area. Also, the systematic research is intentionally restrictive in order to demonstrate the importance of chronopharmacology in rheumatoid arthritis.

According to the findings, the formulation of modified-release prednisone (MR), when used at night, provided significant improvements in symptoms, allowing an optimization of time and dosage of drugs, better quality of life for patients affected by the disease and regression of the pathology. Thus, it is evident that the use of chronopharmacological principles in the pharmacological treatment of rheumatoid arthritis needs to be taken into account in clinical discussions.

Finally, through this review, possible solutions for the application of chronopharmacology in the clinical practice of pharmaceutical professionals and other health professionals were also mentioned, aiming at incorporating this science as a patient safety strategy.

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